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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,842	SERRERO, GINETTE	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-85* is/are pending in the application.

4a) Of the above claim(s) *13-19,40-44 and 66-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 20-39, 45-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Election/Restrictions

Claims 13-19, 40-44, and 66-85 **remain withdrawn** for the reasons set forth in the previous Office Action (Paper No. 12) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-85 are pending and claims 1-12, 20-39, and 45-65 are ~~pending and~~ examined on merits. my 9-11-03

Claim Rejections - 35 USC § 103

Claims 1-12, 20, 21 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over Shoyab et al (WO 91/15510).

Applicant argues that Shoyab et al teach away from the instant invention, i.e. following Shoyab et al's teaching would lead to an incorrect diagnosis of patient not having tumor instead of having tumor, and the instant claims recite that the ratio of GP88 positive cells to the total number of cells in a biological sample is indicative of tumorigenicity. This examiner does not fully understand applicant argument that the instant claims recite that the ratio of GP88 positive cells to the total number of cells in a biological sample is indicative of tumorigenicity. The ratio (# GP88 positive cells/ # total cells) could be from 0 (no positive) to 1 (all of the cells are positive) and therefore if any ratio is indicative of tumorigenicity, then sample with no GM88-positive cells would indicate tumorigenicity; this does not make very much sense. Since the conclusion step does not make very much sense, this examiner will analyze the determination step against the prior art. Applicant argument is not convincing because the active steps of instant claims are drawn to determining how many cells are positive for GP88 and determining a ratio (#GP88 positive cells/total cells) and making conclusion that any ratio would indicate tumorigenicity (since this step is just making decision and the instant claims and applicant's argument does not make very sense to this examiner, this

step is not included in the obviousness analysis). As for a reasonable expectation of success argument, this examiner is not able to address because instant specification does not teach what is meant by ratio of GP88 positive cells to the total number of cells in a biological sample is indicative of tumorigenicity and it could mean anything,

Shoyab et al teach the amino acid sequence of GP88 protein (Shoyab et al call it epithelin precursor), the production of antibodies by the immunization of animals using epithelins or synthetic epithelin peptides (p. 18), the expression of epithelin of in various tissues of mice and humans, such as kidney, breast, testis, and ovary (p. 23), "the presence and levels of epithelin in body fluids and tissues may directly or inversely relate to the presence and pervasiveness of certain cancers and other growth related diseases," and assays which can detect and/or quantify epithelins may be used in diagnosis and prognosis of growth related disease (p. 30), and also teach a mature of epithelin is involved in stimulating growth of certain cells (see abstract). Shoyab et al (WO 91/15510) do not teach away from the instant invention as applicant alleges, i.e., Shoyab et al do not teach that epithelin precursor is a growth inhibitory molecule. Rather, Shoyab et al teach epithelin 2 (a mature form of the precursor) is a growth inhibitory molecule.

Since Shoyab et al teach all of the necessary reagents used in the instant invention and teach possible link between expression level of epithelin and cancer, one of ordinary skill in the art at the time the invention was made would have been motivated to determine if expression levels of epithelin could be used as biomarker for cancer because cancer diagnosis using a biomarker is cheaper and fast.

Rejection of claims **22-39, 45-65** drawn to cancer diagnosis with the specific ratio of GP88 positive cells to the total number of cells in a biological sample, or method of determining whether a patient is resistant to anti-estrogen therapy **is withdrawn** because applicant argument is convincing.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 20-39, 45-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 20, 21, and 22 are confusing, therefore indefinite. The instant claims recite that the ratio of GP88 positive cells to the total number of cells in a biological sample is indicative of tumorigenicity. The ratio (# GP88 positive cells/ # total cells) could be from 0 (no positive) to 1 (all of the cells are positive) and therefore if any ratio is indicative of tumorigenicity, then sample with no GM88-positive cells would indicate tumorigenicity; this does not make very much sense. Further, claims 22 says that the ratio of about 1 % would indicate tumoriogenicity but the specification, for example at page 52 Paragraph [00129] says that less than 5 % GP88 positive cells is considered negative.

Claim 27, 29-39, and 45 is confusing because it says determining "the amount of GP88" and "the amount of GP88" is indicative of patient's resistance to antiestrogen therapy. If the determining step amount of GP88 is zero, does it still indicate patient's resistance to antiestrogen therapy?

Claim 28 is confusing, therefore indefinite. Claim says that the ratio of GP88 positive cells to the total number of cells in a biological sample is indicative of resistance to antiestrogen therapy. The ratio (# GP88 positive cells/ # total cells) could be from 0 (no positive) to 1 (all of the cells are positive) and therefore if any ratio is indicative of resistance to antiestrogen therapy, then sample with no GM88-positive cells would indicate resistance to antiestrogen therapy; this does not make very much sense

Claim 45 recites the limitation "said number of GP positive cells" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 46 recites the limitation "said ratio" in line 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 20-39, and 45-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for more than 5 % GM88 positive staining for breast cancer diagnosis, does not reasonably provide enablement for (1) ratio or amount of GP88 positive cells and (2) any other cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are interpreted as drawn to any cancer diagnosis or method of determining whether patient is resistant to antiestrogen therapy using a biomarker GP88. The entire specification teaches breast cancer has higher expression of the biomarker but does not teach any other cancer could be diagnosed with the marker. The specification does not present any in vivo data to correlate detection of the marker to growth of any tumor other than breast tumor. Further, Shoyab et al (WO 91/15510) at page 23 says that normal breast tissue expresses the marker, therefore any detection would not lead to diagnosis of breast cancer because normal breast cells also express GP88. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to instant invention. Cancer diagnosis and prognosis of patient's response to certain therapy are not trivial matters. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed)

cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Considering limited guidance, no other working examples other than breast cancer, unpredictability in the art, it is concluded that undue experimentation is required to practice the full scope of the invention.

Claim Rejections - 35 USC § 101

Double Patenting

Claims 1-12, 20-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20, 28-56 of copending Application No. 09/456,886. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to method of cancer diagnosis using the same biomarker.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

Claim 65 is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-

308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
January 13, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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